Appendix 1

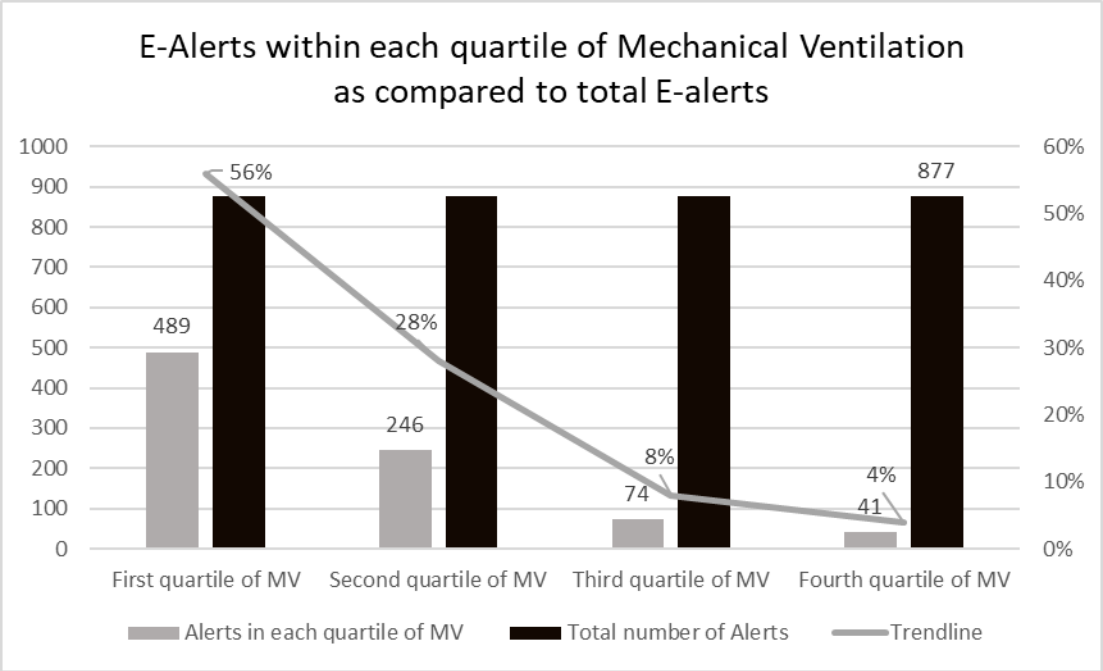
Development of E-Alerts

Firstly, we would like to discuss the development of the electronic alert strategy. E-alerts were created in EPIC health systems (version 2013) by the biomedical informatics research team at the Ohio State University. A base best practice alert was generated which reviewed data from the bedside monitor (for SpO_2 levels) and mechanical ventilator (for FiO_2 levels) every five minutes. A limit of five minutes was chosen to limit large volumes of data limiting efficiency and with the presumption that values within five minutes represent clinical continuity. The effort in the development of this alert represents a multidisciplinary integration of various work groups, including physician investigators, the ICU oversight team, and respiratory therapy and nursing oversight along with the biomedical informatics research team. A modified Delphi technique was used with multiple iterative refinements during the development of this alert to estimate the final goals. Assessment of fluidity of workflow and resources to provide the least interruption to providers while maintaining scientific merit were the core goals. In addition, we focused on the development of this tool in a manner to best assist in generalization of this alerting mechanism through EPIC health systems or other health systems.

Results

877 alerts were sent on 72 patients. 84% were initiated in the initial half (first two quartiles) of mechanical ventilation and the alert rate declined progressively [First quartile (56%) second quartile (28%), third quartile (8%) and fourth (4%)].

Figure Appendix 1.1



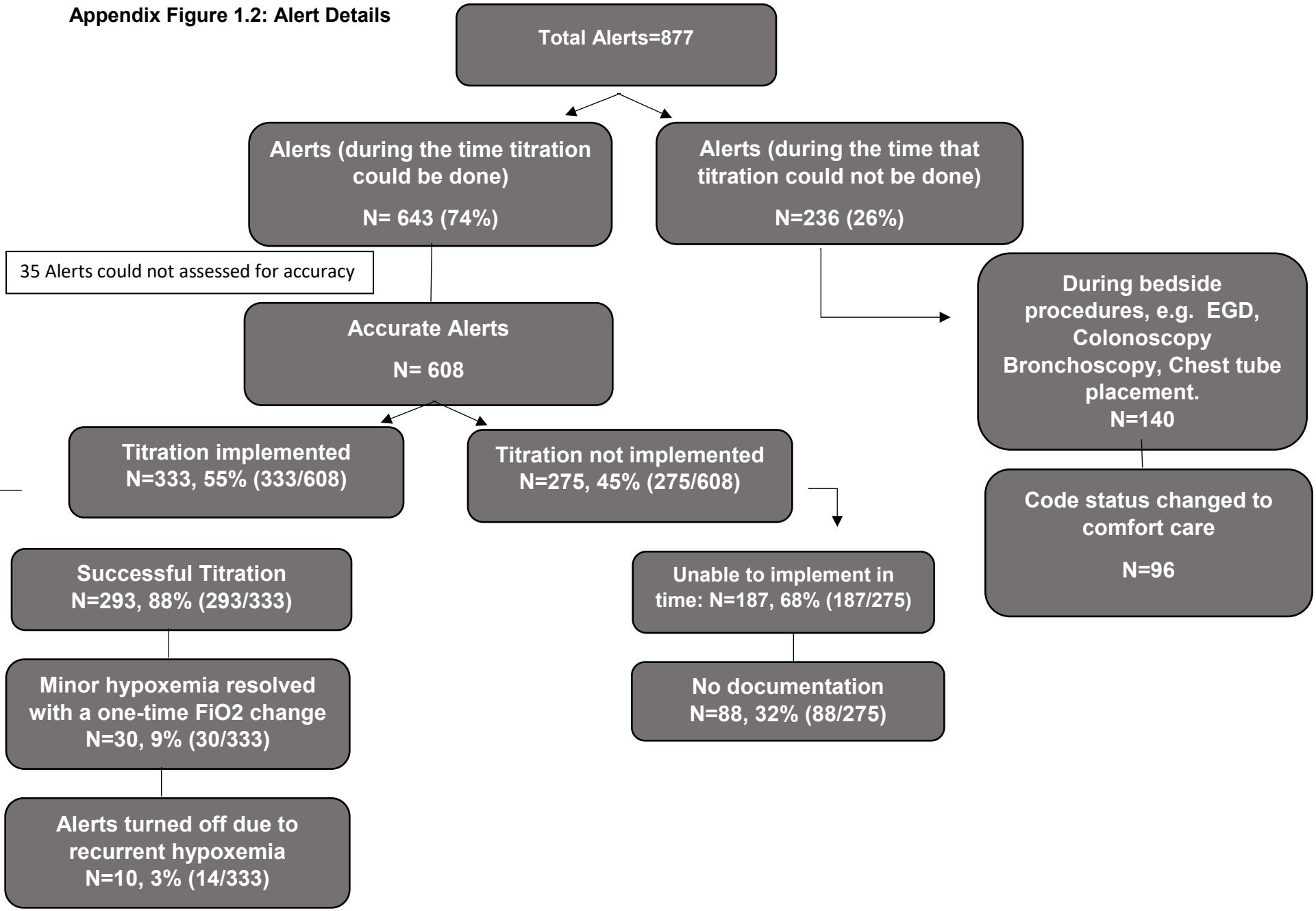
When patients (N=38) in whom all alerts were within the first half of duration of mechanical ventilation (first two quartiles) were compared to those without alerts or those in whom alerts were spread out (N=97), both mechanical ventilation days and ICU days were reduced.

All alerts in the first half	**N=38**	**N=97 (Intervention + Control)**	**P value**
MV duration, days	2 (1 - 4)	3 (2-5)	0.02
ICU LOS in days	4.7 (3.2-10)	9.5 (6-16.6)	0.002

Among all the 877, 643 (74%) were sent at a time where respiratory therapists could attempt titration. Each alert for assessed for accuracy by a blinded personnel. 35 Alerts could not be assessed due to EPIC related issues with missing data retrospectively. Among 608 accurate alerts, titration was implemented in 55% (N=333/608) and was successful in 88% (N=293/333). In 30 instances (9%), hypoxemia (SpO2<88%) was reversed by a one-time increase in FiO_2 without any other intervention. In 10 instances (3% alerts, 5 patients) then alerts had to be turned off due to recurrent hypoxemia and inability to maintain Spo2 within 88-92% range. On further evaluation, the patients in whom alerts had to be turned off were those with acute respiratory failure due to acute exacerbation of idiopathic pulmonary fibrosis with bilateral multilobar pneumonia; acute exacerbation of pulmonary vasculitis associated with rheumatoid arthritis; diffuse alveolar hemorrhage in the setting of acute leukemia; two patients with acute respiratory distress syndrome.

Respiratory therapists did not implement titration after 45% (N=275/608) alerts. We attempted to find reasons for the same. Documentation of why titration was not done was encouraged throughout the study. In 187 instances, respiratory therapists stated that they were not able to implement titration because; 1) they could not get to the patient in time; 2) occupied with other critical procedures/ care for other patients they were assigned in that shift. We were not able to find documentation in 88 instances. We analyzed the alerts which were not documented; in 76 of 88 of those instances, had borderline range values (FiO_2 between 50-60% and SpO_2 =93 or 94%).

Appendix Figure 1.2: Alert Details



Criteria for alert to fire (the following must be true):

1. Oxygen level - FI02 greater than or = to 50% or 0.5 and Oxygen saturation in blood - SpO2 greater than or = to 92%
2. Patient has status of “enrolled” in the research studies activity for study 2014H0236 [2014H0236]
3. Patient is intubated, attached to a device, and respiratory flow has started
4. Patient is in an inpatient hospital encounter
5. Patient is located on one of the following units

Encounter limitation inclusions:

	Service Area	Location	Department	Department Grouper	Encounter Type
1	OSU WEXNER MEDICAL CENTER [1000]	JAMES [200003]	C11C [300101303]		Hospital Encounter [3]
2	OSU WEXNER MEDICAL CENTER [1000]	JAMES [200003]	C11D [300101304]		Hospital Encounter [3]
3	OSU WEXNER MEDICAL CENTER [1000]	JAMES [200003]	C11G [300101307]		Hospital Encounter [3]
4	OSU WEXNER MEDICAL CENTER [1000]	JAMES [200003]	C11H [300101308]		Hospital Encounter [3]
5	OSU WEXNER MEDICAL CENTER [1000]	JAMES [200003]	C14B [300101309]		Hospital Encounter [3]
6	OSU WEXNER MEDICAL CENTER [1000]	UNIVERSITY HOSPITAL [200001]	KMCU [300101764]		Hospital Encounter [3]

6. Patient must be attached to device for at least one hour before the first alert will fire
7. Pages are not to be sent more frequently than every 30 minutes
8. A page will be sent every 30 minutes while conditions exist
9. Once conditions are no longer met, (or patient is extubated), no further pages will be sent

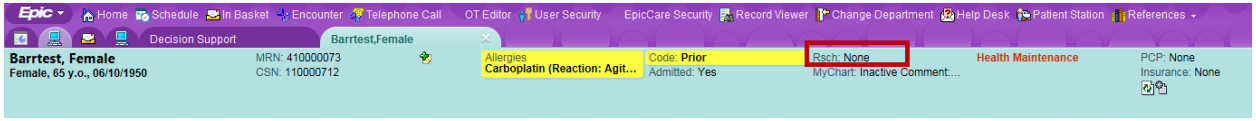
Workflow:

Patient is identified as being a part of the research study

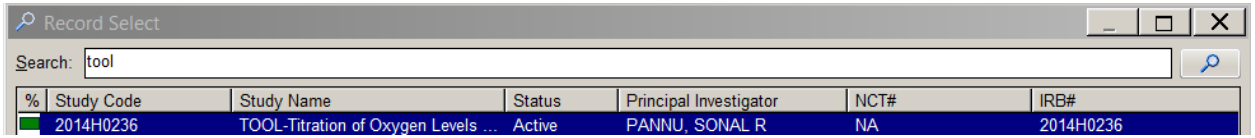
Control patients will be identified and flagged using a manual process to be determined by Dr. Pannu

Non-control patients will be linked to the research study using the research studies activity in IHIS

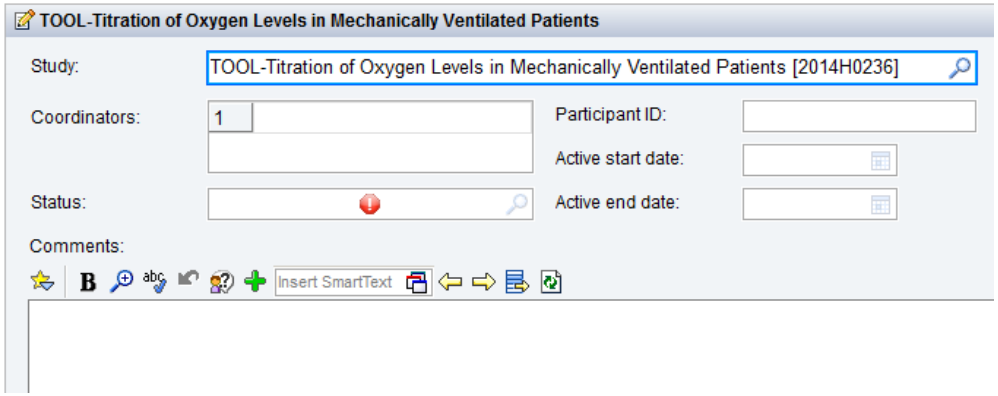
1. Select the research studies activity link from the patient header



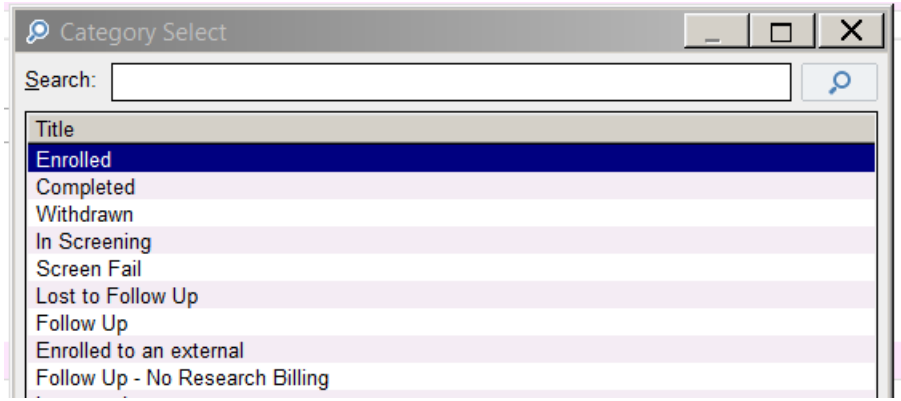
2. The research studies activity will open. Select study from the list of available studies. Note: Only staff members that are listed as being members of the study team in IHIS will be able to select this study. Please contact research.billing@osumc.edu to have staff added to the list.



Fill out the following fields: Study, Coordinator (choose your name from the list), Start Date, and Status of “Enrolled”.

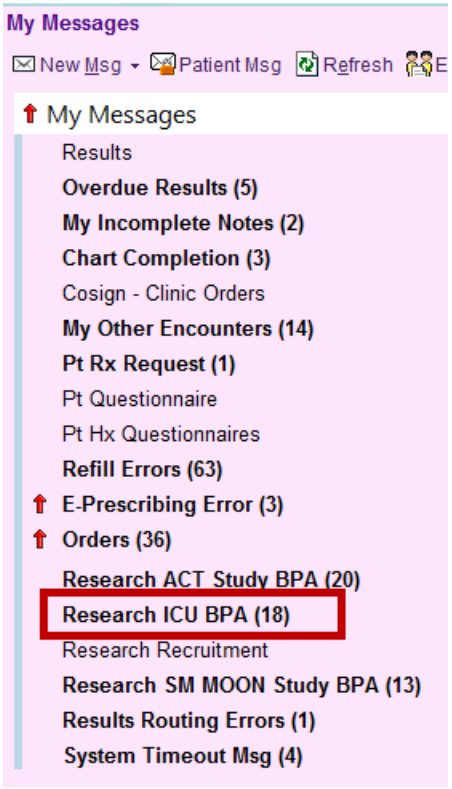


The enrollment statuses appear in IHIS as follows:

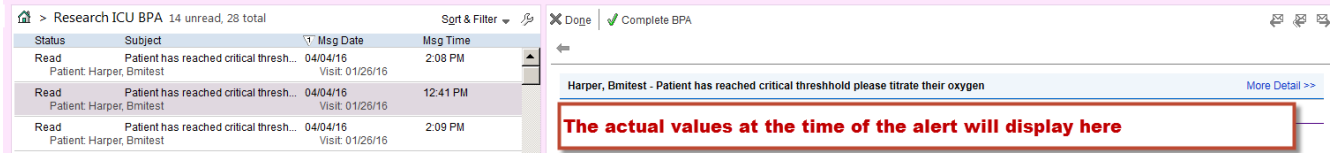


Select "enrolled" for the non-control patients, and **"in screening"** for the control patients. A patient with any other status except for "enrolled" should not receive the alert.

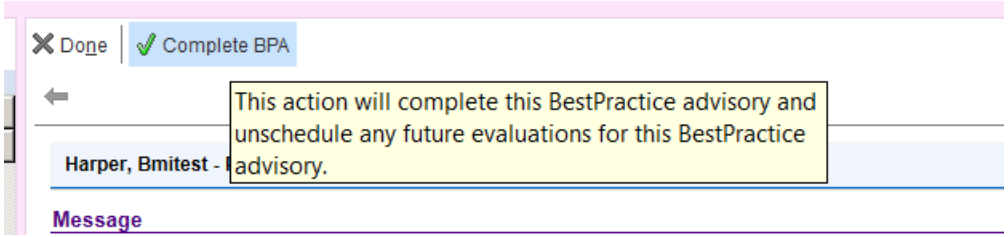
3. Once a patient is enrolled, if the criteria for the alert is met, you will not receive a pop up window on your screen like a typical BPA. You will receive a page/message on the Cisco phone/pager as assigned. The page will state the following: "Room*/Bed # This is a research study notification for the ICU Blood Oxygen protocol. Please log into IHIS to check your inbasket messages for more information*"
4. A message is sent to the inbasket at the same time that the page is sent. The inbasket message will appear in a new folder type - Research ICU BPA folder



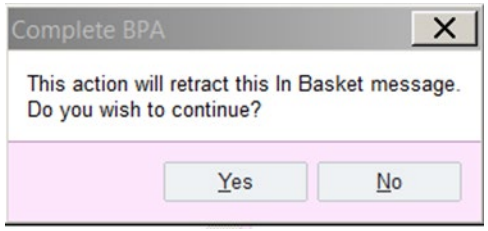
The details of the message will display as follows:



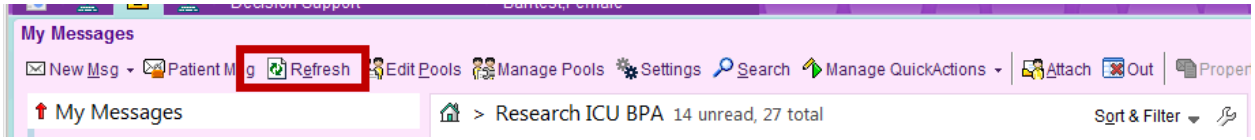
5. **The recommended way to address the alert** is to select “Complete BPA” first, which will stop the alert (and the pages), and no additional pages will fire unless the patient meets the conditions again after 30 minutes have passed



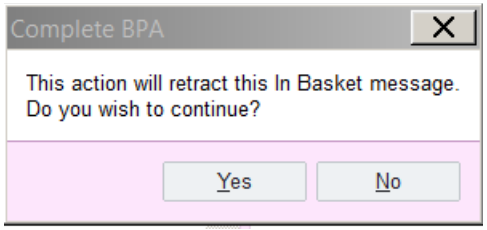
Then you will see this pop up window, and select Yes to stop the alert.



Then select the refresh button, and the message will fall out of view for all participating staff members

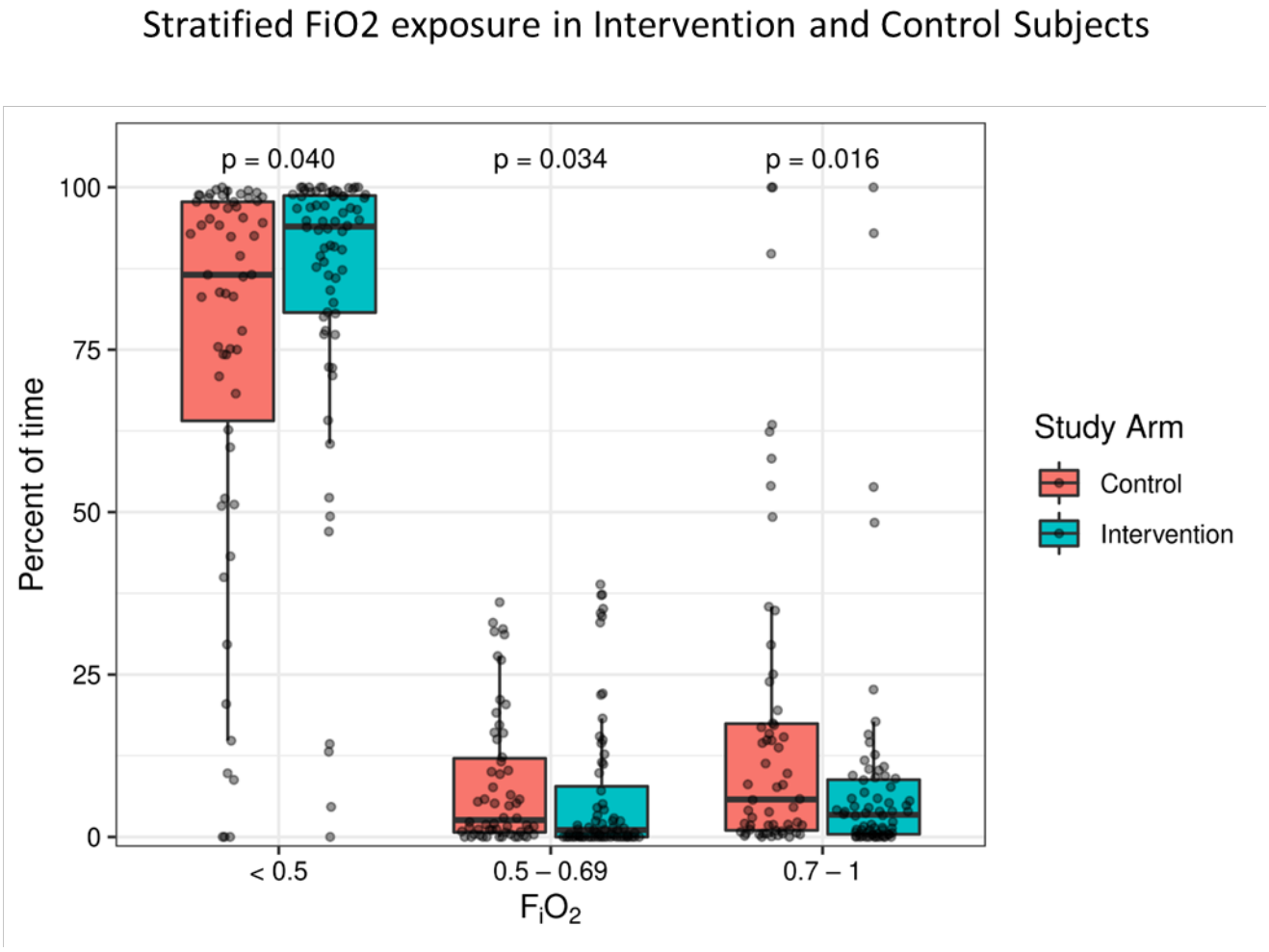


6. ***Not the recommended way:** If you double click on the message to open it, you will receive this pop up window, which will take the message out of the inbasket for all members of the pool, and will retract the but the alert has not been stopped

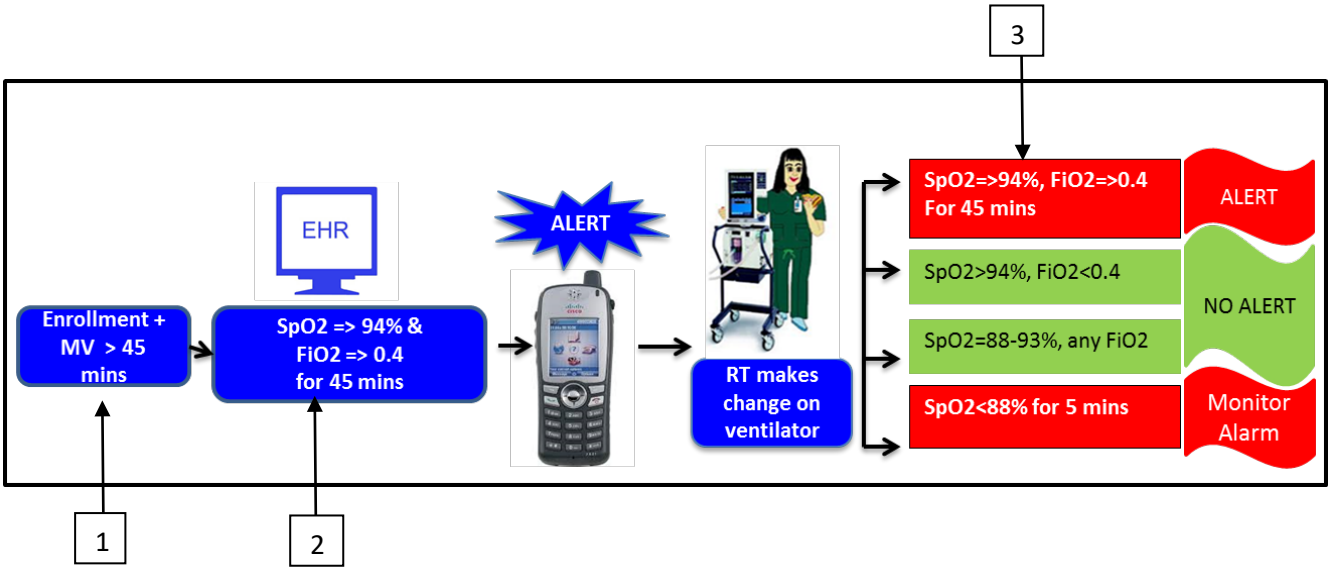


7. Once a patient is unattached from the vent, or no longer enrolled in the study, the alert is no longer eligible to fire.

Appendix Figure 2



Appendix Figure 3: Changes in the Interventional Flow Diagram based on the Pilot Data



Title: **Titration of Inspired Oxygen during Mechanical Ventilation using an Electronic Alert based Protocol and Bedside Decision Support Tool**

Acronym: TOOL

Funder: Center of Clinical and Translational Science, Davis Bremer Pre-K Award and KL- 2, through National Center for Advancing Translational Sciences

Protocol: Version 5

Date: September 18, 2020

PROTOCOL SUMMARY

This protocol consists of progressive studies to identify oxygenation practice for mechanically ventilated patients in the intensive care unit and study the feasibility and preliminary efficacy of an electronic-alert (e-alert) based oxygen titration protocol and supporting bedside decision support tool.

Phase 1 of this protocol refers to an observational retrospective evaluation of liberal vs conservative oxygenation practices.

Phase 2 of this protocol refers to prospective studies, divided into a pilot phase (TOOL-1) for feasibility of the e-alerts based oxygen titration protocol followed by a randomized clinical trial (TOOL-2) to study preliminary efficacy of the oxygen titration protocol.

CURRENT STATUS: Phase 1 (N=50) and Pilot Study (TOOL-1, N=100) are completed and preliminary data is included in the protocol. The larger randomized clinical trial (TOOL-2, N= 316) is registered and currently pending initiation. (NCT04481581; Clinical Trials. gov).

STUDY SUMMARY

Title	**T**itration **O**f Inspired **O**xygen **L**evels during Mechanical Ventilation using a Bedside Decision Support Tool (TOOL)
Background	Hyperoxia has been associated with higher mortality in intensive care unit (ICU) patients and is known to augment ventilator-induced injury. It also has worse outcomes in post cardiac arrest, COPD, post- stroke, as well as, post congestive heart failure patients. Literature reports of liberal oxygen titration practices in the ICU, associated with higher morbidity and mortality. Therefore, there is a critical need to institute measures to improve practice of fractional oxygen (FiO2) supplementation in a precise range to maintain optimal oxygen saturation (SpO2).
Objectives	PHASE1: To determine the duration and extent of conservative versus liberal FiO2 practice in all mechanically ventilated patients in the medical ICU
	PILOT (TOOL 1): To determine the feasibility and safety of an electronic–alert (e-alert) based oxygen titration protocol with bedside decision support.
	RCT (TOOL 2) Primary Objective: To determine the efficacy of an electronic-alert based oxygen titration protocol on reducing excessive oxygen exposure (i.e. FIO2 ≥ 0.4 when SpO2 ≥ 94%) during mechanical ventilation. Secondary Objectives: To determine the effect of an electronic-alert based oxygen titration strategy on duration of mechanical ventilation and other hospital based outcomes.
Study Design	PHASE1: Retrospective Observational Study of all mechanically ventilated patients in the medical ICU
	PILOT (TOOL 1): A Pilot Randomized Clinical Trial to determine feasibility and safety of an e-alert based oxygen titration protocol
	RCT (TOOL 2): A Single Center, Unblinded, Randomized Clinical Trial to determine efficacy of an e-alert based oxygen titration protocol
Intervention group	PHASE1: N/A
	PILOT (TOOL 1): All consented mechanically ventilated patients in the medical ICU have oxygen titrated by an e-alert based oxygen titration protocol with decision support to titrate FiO2 to maintain SpO2 between 88-92%
	RCT (TOOL 2): All consented mechanically ventilated patients in the medical ICU have oxygen titrated by an e-alert based oxygen titration protocol with decision support to titrate FiO2 to maintain SpO2 between 88-94%

Delivery of Intervention	PHASE1:NA
Delivery of Intervention	PILOT (TOOL 1): Respiratory therapists will receive electronic alerts on their cisco phones if **SpO2 ≥ 92 % and FiO2 ≥ 0.5 at every 30 minutes** after initiation of the protocol. They will respond to the alerts by reducing FiO2 on the ventilator per decision support provided for the study. FiO2 and SpO2 monitoring by electronic alerts will continue for the duration of mechanical ventilation. Respiratory therapists will continue to receive alerts if FiO2 and SpO2 criteria remain over the target range. Once FiO2 and SpO2 are within the target range, no alerts will be generated.
	RCT (TOOL 2): Same as for TOOL 1 with the following changes in the FiO2 and SpO2 criteria, fidelity and duration of alert timing based on preliminary data. Respiratory therapists will receive electronic alerts on their cisco phones if **SpO2 ≥ 94 % and FiO2≥ 0.4** for 80% of the recorded values every minute within a 45 minute interval. The alert would screen data every 45 minutes.
Control group	PHASE1: NA
	PILOT (TOOL 1): All consented mechanically ventilated patients in the medical ICU have oxygen titrated per current standard of care (**SpO2=88-92%, titrate FiO2 at least every 4 hours).** Physician place oxygen titration orders in EMR and respiratory therapists conduct FiO_2 titration without electronic alerts.
	RCT (TOOL 2): Control group remains the same as for TOOL 1
Sample size	PHASE1: N=50
	PILOT (TOOL 1): N=100
	RCT (TOOL 2): N=316
Inclusion Criteria	PHASE1: mechanical ventilation in the medical ICU
	PILOT (TOOL 1): Age > 18 years Presence of mechanical ventilation
	RCT (TOOL 2): Age > 18 years Presence of mechanical ventilation
Exclusion Criteria	PHASE1: NA
	PILOT (TOOL 1) Pregnancy Prisoner status Pneumothorax Carbon monoxide poisoning Hyperbaric oxygen therapy Acute ST elevation Myocardial Infarction
	RCT (TOOL 2): Mechanical ventilation greater than 6 hours prior to enrollment Initiation of mechanical ventilation at another hospital Pregnancy Prisoner status Pneumothorax

	Carbon monoxide poisoning Hyperbaric oxygen therapy Acute ST elevation Myocardial Infarction Diagnosed COVID 19 infection
Randomization	PHASE1: NA
	PILOT (TOOL 1): Patients will be randomized in a 1:1 ratio to intervention vs control arm
	RCT (TOOL 2): Remains same at the TOOL 1
Blinding	PHASE1: NA
	PILOT (TOOL 1): Unblinded
	RCT (TOOL 2): Respiratory Therapists and Study coordinators will be unblinded. Study Investigators, medical monitor and statistician will be blinded.
Primary Outcome	PHASE1: Proportion of liberal oxygenation practice in the ICU
	PILOT (TOOL 1): Feasibility of implementing the protocol Safety of the e-alert based oxygen titration protocol
	RCT (TOOL 2): The primary outcome is the proportion of time during mechanical ventilation spent with FiO2≥0.4 and SpO2≥94%.
Secondary Outcomes	PHASE1: NA
	PILOT (TOOL 1): Preliminary efficacy of the e-alert based oxygen titration protocol
	RCT (TOOL 2): Proportion of time during mechanical ventilation spent with SpO2<88% Duration of mechanical ventilation Length of ICU stay Length of hospital stay Hospital mortality
Statistical Consideration and Analysis	PHASE1: percent and means with standard or median between the conservative and liberal practice groups will be reported. Logistic regression will be used to identify predictors.
	PILOT (TOOL 1): Feasibility assessed by recruitment and alert compliance. Two-sample T Test/Wilcoxon rank sum test for secondary outcomes.
	RCT (TOOL 2): The primary analysis will be an intention to treat comparison of the primary outcome between subjects in the intervention vs control arms. Differences in the primary outcome between the two study arms will be tested using either a two-sample t-test, if the outcome is normally distributed (p-value from Shapiro-Wilk test > 0.05), or the Wilcoxon rank-sum test (p-value from Shapiro-Wilk test < 0.05). A $\alpha = 0.05$ level for statistical significance will be used for testing differences in the primary outcome between groups.

Human subjects/DSMB	PHASE1: NA
	PILOT (TOOL 1): The trial will be conducted with a deferred consent as the study cannot practically be carried out without this measure with scientific merit:
	RCT (TOOL 2): Similar consenting procedure. The OSU CCTS-supported Data and Safety Monitoring Board will oversee the study.

1. BACKGROUND

In recent years, there has been mounting evidence of the adverse effects of hyperoxia. Hyperoxia induces cell damage through production of reactive intermediates of oxygen production called "free radicals".[1,2] Since oxygen is inhaled, pulmonary oxygen toxicity is more marked. It manifests as a spectrum from subclinical cellular changes such as reduction in capillary endothelial cells, surfactant, macrophage function and mucociliary function to clinical manifestations of tracheobronchitis, absorption atelectasis, pulmonary edema and fibrosis.[1,3,4] Oxygen toxicity is implied in conditions like, respiratory distress syndrome, bronchopulmonary dysplasia, ischemia, reperfusion lung injury and certain drug induced pulmonary diseases.[4] Hyperoxia has been associated with higher mortality in intensive care unit (ICU) patients and is known to augment ventilator-induced injury. It also has worse outcomes in post cardiac arrest, COPD, post- stroke, as well as, post congestive heart failure patients. However, stringent practices for titrating supplemental oxygen are not observed. The amount of oxygen causing pulmonary damage is not precisely known. However, it is noted in both animal and human studies that fractional oxygen (FiO_2) of greater than 0.5 is associated with worsening lung injury.[5,6] Peripheral oxygen saturations (SpO_2) and arterial oxygen tension (PaO_2) are used commonly for FiO_2 titration. The NIH/NHLBI ARDS Network recommends a lower target of 88% for the lower Spo2 target range and upto 95% for the upper target range. Recent studies recommend avoiding additional oxygen supplementation for SpO2 above 94- 96%.

Prevention of hyperoxia is necessary. Recent data shows poor outcomes associated with FiO_2 as high as 0.4.[7] In a large retrospective study of all ICU patients in the Netherlands, high FiO_2 (>0.5) in the first 24 hours of admission was linearly related to mortality. Both high and low PaO2 were associated with mortality.[5] In the same study, the in-hospital mortality was independently related to the mean FiO_2. In addition, changes suggestive of oxidative stress were noted in human bronchoalveolar fluid after exposure to 0.5 FiO_2 for 44 hours.[8] Also, higher mortality was seen in post cardiac arrest patients who were hyperoxic.[9] More recently, hyperoxia was clearly associated with higher mortality even in patients in the neuro-critical care unit who were mechanically ventilated after having stroke.[10] Similarly, a large prospective study in Australia reviewing oxygen supplementation to COPD patients prior to reaching the hospital, found that liberal oxygen supplementation correlated with higher mortality[11]. Also, higher long term mortality was seen in patients with abdominal surgery who were hyperoxic. [12]

Most healthcare staff agree that oxygen titration is overlooked and needs further education and research. There have been attempts to systematically address oxygen titration[13]. A "goal directed oxygen strategy" which consists of daily physician orders to maintain SpO2 within predefined goals led to target SpO2 only 60% of the time. The authors highlighted that the results were unrelated to nursing workload or night team exhaustion[14]. Use of methods like a

"silicone band" on the patient's arm stating oxygenation goals" resulted in moderate compliance and variable oxygenation[15]. Both these studies, indicate that "one-time orders or indicators" are not effective. As such, a specific and directed strategy is called for.

The preceding citations and related discussion illustrate that there is a critical need to establish an effective and precise FiO_2 titration strategy, which is the goal of this study. In order to achieve targeted oxygenation, we propose the use of "electronic medical records-based surveillance" which can ascertain oxygenation real time and send alerts via pagers or phones to respiratory therapists. A decision support tool will be provided with directions for precise titration. Electronic "assistance" through electronic medical records or computerized decision support in the ICU has widely helped improve compliance to guidelines, e.g. low tidal volumes, detection and management of sepsis, etc.[16,17]. These electronic alerts for oxygen titration will serve as real time "reminders" without increasing their workload. Cochrane Effective Practice and Organization of Care (EPOC) Review Group list "reminders" as a specific professional intervention for implementing a change in practice or in provider behavior. Eighteen reviews looked at "Reminders" alone as an intervention, both paper and computer-based clinical decision support systems and have found them about 73-78% effective at creating an effective change in provider behavior[18]. Our approach of using reminders and decision support, is supported by the normalization process theory for implementation of interventions[19,20]. The normalization process theory has been previously applied as a theoretical framework for implementation of electronic health systems and guidelines[19,21]. Thus, we expect that electronic health records based automated electronic-alerts (E-alerts) that ascertain real-time oxygenation based on SpO_2, can serve as continuous reminders to address the above need. We propose this approach with the assistance <u>of an oxygen titration protocol consisting of e-alerts via EMRs as a reminder for titration and decision support to guide oxygen adjustment.</u>

2. STUDY OBJECTIVES

2.1. *PHASE 1*

2.1.1. To determine the duration and extent of conservative versus liberal FiO2 practice in all mechanically ventilated patients in the medical ICU

2.2. *PHASE 2*

2.2.1. *PILOT (TOOL 1):* To determine the feasibility and safety of an electronic–alert (e-alert) based oxygen titration protocol with bedside decision support.

2.2.2. RCT (TOOL 2):

Primary Objective: To determine the efficacy of an e-alert based oxygen titration protocol on excessive oxygen exposure (i.e FIO2 $\geqslant$ 0.4 when SpO2 $\geqslant$ 94%) during mechanical ventilation.

Secondary Objectives: To determine the effect of the electronic-alert based oxygen titration strategy on duration of mechanical ventilation and other hospital based outcomes.

The central hypothesis is that the use of a respiratory driven oxygen titration protocol will reduce hyperoxia and reduce hours on mechanical ventilation as compared to a traditional physician based approach. We plan to titrate within the ranges of current physiologically accepted oxygenation targets of 88 - 94% and aim to reduce FiO_2 exposure to 0.4 or below. [8]

3. PRELIMINARY STUDIES

Preliminary Data in support of Phase 1 and Phase 2

We found that in a tertiary care ICU conservative titration practices for mechanically ventilated patients with acute respiratory distress syndrome were not practiced. 210 patients met the inclusion criteria, 155 (74%) were exposed to excessive FiO2 for a median duration of 17 hours (interquartile range 7.5-33 h). Prolonged exposure to excessive FiO2 correlated with worse oxygenation index (combined index of arterial oxygen tension, supplied FiO_2 and mean airway pressure) at 48 hours in a dose-response manner ($p < .001$). Both exposure to higher FiO2 and longer duration of exposure were associated with worsening oxygenation index at 48 hours ($p < .001$), more days on mechanical ventilation, longer ICU stay, and longer hospital stay ($p = .004$). $_2$.[22]

Phase 1 data in support of Phase 2:

Electronic chart review conducted in the Ohio State University, medical ICU presence of liberal oxygenation as described above ($FiO_2 > 0.5$, SpO2 **≥** 92%) was present in over 40% of the mechanically ventilated patients (N=50). Among the patients exposed to liberal oxygenation with the above criteria, 50% of those had excessive oxygen supplementation, (SpO2> 95%, FiO_2> 0.5).This practice persisted in spite of the ICU mechanical ventilation protocol limiting SpO2 to 88-92%. We presume the reasons for this to be one time physician orders, current protocol determines that changes should be made every 4 hours and lack of prioritization of titration.

4. STUDY DESIGN

4.1. Design summary

4.1.1. *Phase 1:*

The first phase of the study involves a formal observational analysis of FiO2 practice in mechanically ventilated patients in the medical ICU, focusing on degree and duration of conservative vs liberal FiO2predictors of practice, patient characteristics, and ICU outcome based data including, ventilator days, ICU stay and mortality. For phase 1, acceptable oxygen saturation ranges from 88-92%. Liberal FiO2 practice will be defined as use of FiO2 of ≥ 0.5 when SpO2 > 92% by non-invasive peripheral sensing monitors. Practice of FiO2 will be categorized as conservative if use of FiO2 <0.5 when SpO2 is ≤ 92%. Phase 1 is being done to formally document the current practice regarding oxygen titration in the medical ICU.

4.1.2. *Phase 2:* The second phase consists of a pilot study followed by a randomized clinical trial. Both the pilot study and the randomized clinical trial have the same trial design.

TOOL 1: A pilot randomized clinical trial to determine feasibility and safety of an e-alert based oxygen titration protocol.

TOOL 2: A single center, unblinded, randomized clinical trial evaluating e-alerts based oxygen titration strategy to determine efficacy of an e-alert based oxygen titration protocol.

Since the pilot, TOOL 1 is completed, we have included the pilot data in the preliminary data section above.

4.2. Study subject selection:

Phase 1 and Phase 2

Studies will take place in the Medical ICU, 10th and 11th Floor. All patients admitted to the ICU will be included, i.e. mechanical ventilation (MV) on admission or admitted patients who require intubation and mechanical ventilation for at least 24 hours. There is a closed group of respiratory therapists, nurses and physicians practicing in this unit and therefore will be relatively homogenous group for the study. Similarly, patients admitted here have comparable medical conditions and comorbidities and therefore will be favorable for the study.

4.3. Inclusion Criteria

4.3.1. *Phase 1*

Age > 18 years
Presence of mechanical ventilation

4.3.2. *Phase 2*

TOOL 1

Age > 18 years
Presence of mechanical ventilation

TOOL 2

Age > 18 years
Presence of mechanical ventilation

4.4. Exclusion Criteria:

4.4.1. *Phase 1 : None*

4.4.2. *Phase 2: TOOL 1*

Pregnancy
Prisoner status
Pneumothorax
Carbon monoxide poisoning

Hyperbaric oxygen therapy
Acute ST elevation Myocardial Infarction

4.4.3. Phase 2: TOOL 2

Mechanical ventilation greater than 6 hours prior to enrollment
Initiation of mechanical ventilation at another hospital
Pregnancy
Prisoner status
Pneumothorax
Carbon monoxide poisoning
Hyperbaric oxygen therapy
Acute ST elevation Myocardial Infarction
Diagnosed COVID 19 infection

4.5. Justification of Exclusion Criteria

Patients with pneumothorax, carbon monoxide poisoning, hyperbaric oxygen therapy and acute ST elevation myocardial infarction may need liberal oxygenation for therapeutic indications, therefore frequent titrations in these patients may not be justified.

Females who are actively pregnant, as defined by the presence of positive urine or serum pregnancy test, or the patient's personal history of current pregnancy, will be excluded primarily because effects of varying supply of oxygen in the fetus is not known.

Exposure to liberal oxygenation is noted in early hours of intubation and initiation of mechanical ventilation[23]. Therefore, we think it is prudent to exclude patients with mechanical ventilation for greater than 6 hours or transferred from other hospitals. The 6 hour time point is determined based the fact that exposure to high oxygen occurs early after intubation and that our unpublished data that over 6 hours of high oxygen exposure may cause lipid peroxidation in bronchoalveolar fluid. Patients transferred from other hospitals will be excluded as we may not be able define the exposure to oxygen prior to study enrollment.

COVID 19 diagnosis: Clinical care including ventilator management in COVID 19 rooms is bundled to maximize interventions. Entrance to COVID 19 rooms is coordinated to reduce potential exposure and protective equipment utilization. Response to the alert may be delayed for these patients, therefore we think it is prudent to exclude these patients.

4.6. Screening:

4.6.1. Phase 1:

Retrospective, charts screened in EMR.

4.6.2. *Phase 2: TOOL 1 and TOOL 2*

Study coordinators will conduct recruitment and enrollment. Study coordinators will be screening for patients meeting initiation criteria. Respiratory therapists will inform them about patients with initiation of mechanical ventilation to help with patients being enrolled as soon as possible after initiation of mechanical ventilation.

4.7. Subject recruitment and consent process:

4.7.1. *Phase 1: NA*

4.7.2. *Phase 2: TOOL1 and TOOL 2*

All participants in the study will be mechanically ventilated and in the Medical ICU. Enrollment in the study is time sensitive. It has to be completed as soon as possible, preferably within an hour of initiation of mechanical ventilation, but no more than 6 hours after, to prevent excessive oxygen exposure occurring mostly in the early hours. Enrollment for patients already meeting criteria but unable to immediately consent is accomplished by labelling the patient to the study on the EMR. To address this situation, enrollment and randomization is conducted 24/7. We will get informed consent from the patient/ Legal Authorized Representative prior to randomization and initiation of the study, in all possible circumstances. However, in about 30- 40% patients we expect that at the time of enrollment the participants will be unable to give a full informed consent. We understand that getting full informed consent is a process and in this situation, we will request a deferred informed consent / HIPPA authorization from the patient or the LAR.

The reason for requesting deferred consent is that the study cannot practically be carried out without this measure with scientific merit. The aim of the study is to achieve oxygen saturation within a time sensitive manner. In order to prevent excessive oxygen exposure we need to initiate oxygen titration as early as possible, preferably within one hour after endotracheal intubation. This is important as the highest potential for hyperoxia is during the initial hours of mechanical ventilation. In about 30- 40% patients we expect that at the time of enrollment the participants will be unable to give a full informed consent. In such situations, we request a deferred consent (Details about the consenting process are noted in section 10 and 11, in human subjects)

4.8. Early withdrawal of patients:

4.8.1. Phase 1: NA

4.8.2. *Phase 2: TOOL 1 and TOOL 2*

We will be using deferred consent, patients will get enrolled and randomized.

In the event that the LAR/ family denies consent, we will withdraw the patient from the study. Since we will only be collecting data, which is recorded in the process of ICU care; no additional or new data will be collected for research

purposes.

If the family member/ LAR gives consent then we will continue the subject's participation in the study. Then for that subject, at the earliest possible time that mechanical ventilation has been terminated and the participant is free from the influence of sedative medications the consenting process will be repeated to inform him of the study and confirm his permission to use his data for the research. He will be asked to sign on the same consent form/ HIPPA authorization. If he refuses at that time we will withdraw him from the study and will not record his data.

4.9. Randomization and Blinding:

4.9.1. Phase 1: NA

4.9.2. *Phase 2: TOOL 1 and TOOL 2*

Randomization: Randomization will be done as early as possible after initiation of mechanical ventilation. We will randomly allocate patients who are admitted to the medical ICU with mechanical ventilation to either group by a computer-generated list. The randomization will be executed by applying the randomization code to the decision support cards. Block randomization will be done with the help of the study statistician. Blocks of 6 will be made with 3 patients randomized to each arm. Blank cards, identical in size, shape and weight to the decision support cards will be made. All cards will contain the patients study number. Both decision support cards and the blank cards will be placed in sealed opaque envelopes, in order of the randomization code known only to the statistician who generated the coded list. The cards will be placed in the ICU supply room in a closed envelope. When a participant meets eligibility criteria, his name will be noted and a study number will be given. The next envelope in the order will be then opened at the time of entry into the study, i.e. within one hour of mechanical ventilation and the corresponding card will be attached to the ventilator in the patient's room.

Blinding: Respiratory therapists and study coordinators will be unblinded. There is no possible way to carry out the study by blinding respiratory therapists. Study investigators, medical monitor and statisticians will be blinded. The statistician may be unblinded if needed by the DSMB. The study coordinators will de-identify data and send it to the statistician.

5. STUDY INTERVENTION

5.1. Phase 1: NA

5.2. Phase 2:

5.2.1. *Interventional Arm: TOOL 1*

In the intervention arm, e-alerts are sent to respiratory therapists for titration and decision support is provided. For all patients admitted to the ICU who need

mechanical ventilation levels of both FiO2 and SpO2 are recorded in the EMR. Levels of both FiO2 and SpO2 are transmitted from the bedside monitor and mechanical ventilator to an interim server connected to the EMR every minute interval. The biomedical informatics team at the Ohio State University has developed a real-time algorithm, which screened these values at specific time points and fired alerts on meeting criteria.

Alert Criteria: Patients need to meet the following criteria for an alert to be fired.
-Age >18 years
-Patient location in the medical ICU,
-Presence mechanical ventilation for ≥ 60 minutes and
-having a SpO2 target > 92% when the supplied FiO2 levels were ≥ 0.5

E-Alerts search for SpO2 and FiO2 values at every 30 minutes and are fired at every 30 minutes to the respiratory therapy cisco phones if both SpO2 and FiO2 values are above target range. Once an e-alert is fired, it continually cycles for every subsequent 30 minute window for the duration of mechanical ventilation.

Decision Support Tool: The decision support tool is used for FiO2 titration and is based on physiological compatibility and expert opinion. It is in the form of a paper based laminated card attached to the ventilators of the study patients and gives instructions for titration.

Monitoring after Titration: The bedside nurse will conduct monitoring after each titration. They will educated to inform the respiratory therapist or the physician in charge immediately if patient develops hypoxemia (SpO2 less than 88% for 5 minutes). Directions for oxygen titration are included in the decision support tool.

Please see appendix A for TOOL 1 flow chart and decision support tool.

5.2.2. *Interventional Arm: TOOL 2*

The intervention arm is similar to TOOL 1 with the following revisions.

Alteration of target SpO_2 range and FiO_2 goal: SpO_2 titration range increased from 88-92% from 88-94%. The goal of 94% was chosen as it still represents an extended conservative range and will possibly accommodate titration needs in patients with hypoxemic conditions. While we increased the range for SpO_2, we decided maintain a conservative approach to prevent excessive supplemental on the FiO_2 with the lower limit to less than 0.4. Alerts will be initiated within 45 minutes of endotracheal intubation.

Change in E-alert frequency and increasing fidelity: Alert frequency will be changed from every 30 minutes to 45 minutes. More importantly, data generated every minute will be utilized and alerts will be generated based on the cumulative values within 45 minutes. Alerts will fire only if 80% values recorded every minute within 45 minutes are above target range.

Reduction in Alert Fatigue: No more than 4 alerts will be generated within 6 hours per patient

Alert Criteria: Patients need to meet the following criteria for an alert to be fired.
-Age >18 years
-Patient location in the medical ICU,
-Presence of mechanical ventilation for ≥ 45 minutes and
-having a SpO2 target ≥ 94% when the supplied FiO2 levels were ≥ 0.4

E-Alerts search for SpO2 and FiO2 values every minute and are fired at every 45 minutes to the respiratory therapy cisco phones if 80% of values for both SpO2 and FiO2 values within the 45 minute window are above target range. Once an e-alert is fired, it continually cycles for every subsequent 45 minute window to monitor FiO2 and SpO2 values for the duration of mechanical ventilation.

Decision Support Tool: Simplified from TOOL 1 based on respiratory therapy input.

Monitoring after titration: Monitoring will remain the same as for TOOL 1. The bedside nurse will conduct monitoring after each titration. They will be educated to inform the respiratory therapist or the physician in charge immediately if patient develops hypoxemia (SpO2 less than 88% for 5 minutes). Directions for oxygen titration are included in the decision support tool.
Please see appendix B for TOOL 2 flow chart and decision support tool.

Data Variable Extraction: The data variable (FiO2 and SpO2) are collected every 1 minute for e-alert generation, however, for analysis data variables will be extracted only every 5 minutes, to avoid data overload. We presume that analysis of every 5 minutes variables could be assumed as near-real time data.

5.3. Phase 2

5.3.1. Control Arm: TOOL 1:

FiO2 titration: FiO2 titration will be carried out by the current ICU mechanical ventilation protocol. Traditionally, physician places orders for titration and is executed by respiratory therapists. Titration may be done by physicians themselves occasionally. The current ICU protocol states to maintain the SpO2 range between 88-92%. Per the current ICU mechanical ventilation protocol, If SpO2> 92% and PaO2>70 then titration needs to be done atleast every 4 hours or could be done frequently if desired. Documentation is done by either in the EMR.

Monitoring after titration: Will be the same as the intervention arm. The bedside nurse will conduct monitoring after each titration. They will educated to inform the respiratory therapist or the physician in charge immediately if patient develops hypoxemia (SpO2 less than 88% for 5 minutes). Oxygen management will be per current ICU protocol.

5.3.2. Control Arm: TOOL 2: Same as TOOL 1, no changes.

Differences and Similarities in TOOL 1 and TOOL 2 are noted in the Table 1

TABLE 1	TOOL 1 Total N=100	TOOL 2 Total N=316	Control Arm for both TOOL1 and TOOL 2
Sample Size	Intervention arm: 50	Intervention arm:158	Control Arm TOOL 1:50 Control Arm TOOL 2 :158
Titration Goal	88-92%	88-94%	88-92%
Intervention	E-alerts at every 30 minutes if both FiO2 and SpO2 values are above target	E-alerts at every 45 minutes if both FiO2 and SpO2 values are above target	No e-alerts. Titration to take place adlib or atleast every 4 hours.
E-alert Fidelity	Alerts based on SpO2 and FiO2 values generated only at 30 minute interval	Alerts based on SpO2 and FiO2 values generated over 45 minute interval	No alerts
Decision Support	Provided through Study	Provided through Study	Current ICU protocol
Role of Respiratory Therapists	FiO2 titration per alerts	FiO2 titration per alerts	FiO2 titration per ICU protocol
Role of Nurses	Monitoring after each titration	Monitoring after each titration	Monitoring after each titration
Physician Care	Care as usual, no change	Care as usual, no change	Care as usual, no change
FiO2 and SpO2 data variables for analysis	Collected electronically at 5 minute interval	Collected electronically at 5 minute interval	Collected electronically at 5 minute interval

5.4. Study Education and Adherence

5.4.1. Phase 1: NA

5.4.2. Phase 2: Similar for TOOL1 and TOOL 2

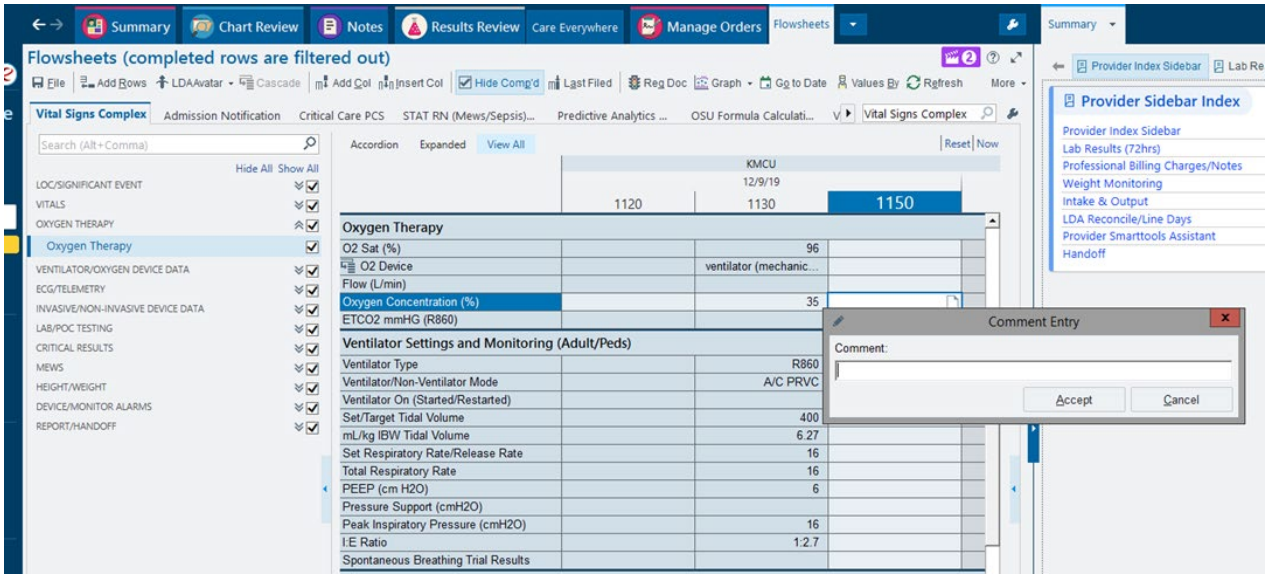
A group of 100 respiratory therapists in the medical ICU, 10th and11th floor within the study period will be the providers. They will be will be educated prior to the onset of the study. This will be done via three modalities. Firstly, in conjunction with the respiratory leadership four educational sessions regarding the study, each lasting for an hour will be held four weeks apart, in an attempt to accommodate for all the respiratory

therapists (on vacation/ sick/etc...). These sessions will also include time devoted to specific protocol related questions that the providers might have. Secondly, details of the study with the titration protocol will be included in the newsletter for the ICU staff for 2 consecutive times before the initiation of the study and once monthly through the duration of the study. Also, a chart with information about the study protocol will be put up in the respiratory break rooms, for the duration of the study.

Adherence: Respiratory therapists will document titration per protocol in the oxygen therapy flowsheet which date/time stamped. (Screen shot below). This is usual practice and will not increase workload. These oxygen titration events will then be correlated with alert date/time stamps during analysis. Primary treating physicians have the right to withhold titration on patients for clinical concerns. If the respiratory therapist has concerns about e-alerts, they need to discuss with the treating physicians or study coordinator. In case of a temporary concern, the alerts will be withheld for a short period. In case of prolonged concerns, they will be held for rest of the period of mechanical ventilation. Respiratory therapists will be advised to document protocol deviations on the flowsheet in the EMR. There is a free text comment section about why titration was not followed. (See screen shot below).

If titration is not done for a specific reason, therapists will be instructed to document the same on the flow sheet in the EMR. If they are performing other critical activities at the time the pager goes off, then they have up to 15 minutes to take action. They may inform other therapists' if unable to reach the patient in time.

In addition, the study coordinator will conduct routine weekly checks on the EMR on study patients to note for protocol adherence or deviation. Spot checks will be made weekly on different days of the week and different shifts. We are hoping to achieve maximum adherence with the above measures in place.



Screenshot for documentation of titration in EMR and free text to note reason for non- compliance

6. STUDY PROCEDURES:

6.1. Data variables:

6.1.1. *Phase 1*: See flow chart and list of data variables listed in Appendix C and D.

6.1.2. *Phase 2: Similar for TOOL1 and TOOL 2*

Please see list of all data variables needed in Appendix E.

Data variables will be collected through the EMR and information warehouse. FiO2 and SpO2 will be extracted at 5 minute intervals to create a real time FiO2 exposure curve and oxygen saturation. Demographics will be used to evaluate similarity between the two groups. APACHE 3 scores, and predicted mortality used for severity of illness on admission. Sofa score on admission and daily will be used to assess organ failures between both groups. Recording of advance directive is necessary to understand reasons of mortality in either group.

Mechanical ventilation related variables used to assess standardization of therapy between both the groups other than supplied O2. Use of FiO2 is higher in patients who are not given neuromuscular blockers, while required in patients with ventilator asynchrony. Therefore, data regarding use of NM blockers is necessary. Also, higher FiO2 may be used for patients with anemia, making data on hemoglobin/ hematocrit necessary.

In addition, for TOOL 2, number of alarms (O2 sat <88% for 5 minutes) per time on study in both groups and time from intubation to randomization will be noted.

6.2. Outcome variables:

6.2.1. *Phase 1*: The outcome for this aim will be prevalence of conservative, as well as, liberal strategy. Also, evaluation of duration and intensity of liberal oxygenation strategy by stratify by FiO2 > 0.5 and > 0.7.

6.2.2. *Phase 2*: *TOOL 1*
Primary Outcome Variable: The primary outcome is feasibility and safety of alerts

Secondary Outcome Variables:
Proportion of time during mechanical ventilation spent with FiO2 ≥ 0.5 and SpO2 ≥ 92%.
Length of Mechanical Ventilation
Length of ICU stay
Length of Hospital stay
Hospital mortality

6.2.3. *Phase 2: TOOL 2*

6.2.3.1. *TOOL 2*
6.2.3.1.1. Primary Outcome Variable: The primary outcome is the proportion of time during mechanical ventilation spent with FiO2 ≥ 0.4 and SpO2 ≥ 94%.

6.2.3.1.2. Secondary Outcome Variables:
Proportion of time during mechanical ventilation spent with SpO2<88%
Duration of mechanical ventilation
Length of ICU stay
Length of hospital stay
Hospital mortality

7. STATISTICAL CONSIDERATIONS:

7.1. Data Analysis

7.1.1. Phase 1

To compare the demographic and co morbid variables of the population within this study, we would estimate the percent (categorical variables) and means with standard deviation (continuous variables with normal distribution) or median (continuous variables with skewed distribution) between the conservative and liberal practice groups. Univariate and multivariate logistic regression will be used to note predictors for conservative vs liberal practice. Odds ratios and 95% confidence intervals will be reported with the estimates.

7.1.2. Phase 2

The primary outcome is the degree of excess exposure measured as the percentage of total mechanical ventilation time with FiO2 ≥ 0.4 and SpO2 ≥ 94%. Normality of the primary outcome variable will be evaluated using the Shapiro-Wilk

test. Differences in the primary outcome between the two study arms will be tested using either a two-sample t-test, if the outcome is normally distributed (p-value from Shapiro-Wilk test > 0.05), or the Wilcoxon rank-sum test (p-value from Shapiro-Wilk test < 0.05). An $\alpha = 0.05$ level for statistical significance will be used for testing differences in the primary outcome between groups, based on intention to treat analysis. Covariate balance between arms will be evaluated using standardized differences. As a secondary analysis to potentially increase power in the trial, we will adjust for baseline covariates that are related to the outcome using inverse probability of treatment weights[24-26]. A similar analysis will be conducted for the proportion of time during mechanical ventilation spent with SpO2<88%.

Length of hospital stay, ICU stay, duration of mechanical ventilation (MV), and in-hospital mortality will be analyzed using competing risks regression, as recommended by several recent articles[27]. Per recommendations, day 0 for all time-to-event analyses will be day of randomization, with MV duration, ICU stay, and overall hospital stay prior to randomization reported and considered as covariates. Cumulative incidence functions will summarize the time-to-event outcomes and estimate the percentage of patients with each outcome (discharged, removed from MV, deceased) by a given day. Differences in cumulative incidence functions between study arms will be tested using Gray's test[26]. Subdistribution proportional hazards regression will estimate hazard ratios between study arms for each outcome[25]. All time-to-event outcomes will be administratively censored at 28 days, since the majority of relevant outcomes occur within this timeframe and durations longer than this can skew results and adversely impact power[24]. Since outcome data are collected as a standard part of a patient's hospital stay, missing data are not expected.

7.1.3. Fidelity Monitoring:

Having the ability to extract covariate real time from the EMR (values every 5 to 15 minutes), fidelity monitoring will be conducted by auditing the EMR for ; 1) Alert accuracy; 2) Percent response to total alerts per patient for the total duration of MV; 3) Percent adherence to directions in the decision support tool. Patients in whom alerts did not work, alerts had to be withheld temporarily or permanently will be included in the intention to treat analysis.

7.1.4. Practice Diffusion:

Practice diffusion may occur to the control group over time. To account for practice diffusion we will analyze the treatment effect in our cohort over sub sequential times through the length of the study. This will be done by including time of enrollment in the regression model for the primary and secondary outcomes and testing for potential interaction between treatment and time of enrollment. Time can be modeled continuously, or divided into intervals for help in interpretation.

8. SAMPLE SIZE

8.1.1. *Phase 1*

We will conduct an observational study for a sample size of 50 mechanically ventilated patients. This is an observational design and the number of participants was determined arbitrarily by the PI and statistician based on number of expected ICU patients with mechanical ventilation in 60-90 days.

8.2. Phase 2

TOOL 1

The sample size for the pilot phase was 100 patients.

TOOL 2

The planned sample size for the trial is 316 subjects, randomized in a 1:1 ratio to the intervention vs. the control arm. The sample size calculation is based on previously published data from similar interventions demonstrating a reduction in the percentage of excess exposure time ranging between 5% and 10% with standard deviations (SD) between 13.5% and 15%[7,28]. With 300 total subjects (150 subjects per arm), there is 82% power to detect a 5% difference with a SD of 15% at $\alpha = 0.05$, based on the two-sample t-test assuming equal variance. This is more conservative than the observed difference in the aforementioned studies (difference = 8%, SD = 13.5%). An additional 16 subjects are included to account for potential 5% loss after recruitment. Since data are collected during a patient's hospital stay, missing data are expected to be minimal.

8.3. **DATA QUALITY MONITORING AND STORAGE:**

Similar for TOOL 1 and TOOL 2

Data from the EMR will be extracted from the information warehouse and entered into a password-secured database by using a predesigned form. This database will be maintained in the pulmonary and critical care drive on a secure server. Paper sheets if any will be kept in a locked cabinet and at the end of the study are disposed using the recycling system for confidential data. Within the database unique identifiers will be assigned to patients and all identifying information will subsequently be removed by the study coordinator.

Data quality will be reviewed remotely using front-end range and logic checks at the time of data entry and back-end monitoring of data using application programming interface tools by the study coordinator.

9. HUMAN SUBJECTS

Similar for TOOL 1 and TOOL 2

9.1. Risks to Human Subjects:

At any time oxygen titration is done, during stand of care or protocol use (either arms)

there remains a chance for desaturations. The protocol does not provide any additional risk for desaturations than the current stand or care. It uses target levels and FiO2 reductions in the degree and range that is current practiced and accepted as standard of care. It is based on current standards, physiologically safe ranges and expert's opinion. The parameters are set with ample safety margins from hypoxic range of peripheral saturation. Also, subjects (in both arms) will be continuously monitored by their bedside nurses In the unexpected situation that desaturation or hypoxemia is noted after titration, steps for oxygen up-titration and directions for informing the physician in charge are present in the decision support tool. The room monitor will alert at a saturation target of 88% for 5 minutes. Further directions to call required help are also noted on the decision support tool. In case of concern of anticipated hypoxia the therapist can contact the study coordinator with appropriate documentation of the reason the titration was not done.

In case of any concerning patient conditions, treating physicians are given the discretion to withhold alert based titration for the necessary period, if they feel necessary. These patients will be included in intention to treat analysis in the arm that they are randomized.

Patient Condition Related Concerns: Patients with the following conditions may have higher oxygen requirements.
a) Acute ST Elevation Myocardial Ischemia: Patients will be excluded
b) Pneumothorax and hyperbaric oxygen therapy: Patients will be excluded
c) Carbon monoxide Poisoning: Patients will be excluded

There is a minimal risk of accidental release of data such as patient information obtained by review of EMR. To minimize this risk, the access to the database will be limited to the study coordinators involved and it will be safe guarded by a password requirement. Once the study is finished, any personal information will be omitted immediately.

9.2. Protection against Risks

9.2.1. Prior to the recruitment of human subjects, this study and a written informed consent document will need to be reviewed and approved by the Biomedical Sciences Review Board of The Ohio State University. The HIPAA Research Authorization Form is not required to be reviewed by the University's IRB, but is subject to audit.

9.2.2. Close monitoring in the ICU: First, the patient will be closely monitored by nursing staff assigned to the patient for 15 minutes after any titration. The nurse patient ratio in OSU ICU's is 1:1 or 1:2, this gives very close and precise monitoring of the patient. The nurse will be educated to inform the respiratory therapist or the physician in case of noted desaturation. Secondly, in a situation where the nurse is not able to connect with a respiratory therapist, they can consult the physicians in charge in case of doubt.

9.2.3. There is a possibility of desaturations or hypoxia after any titration. The goals of titration used the protocol are within well known, previously defined targets is based on sound physiologic principles and supported by recent literature.

Given our pilot data showed some risk of desaturations, we increased the range of our current target for the electronic alert from the previous of 88-92% for 30 minutes to a broader target of 88-94% for 45 minutes. The room monitor will alert at a saturation target of 88% for 5 minutes. In case of concern of anticipated hypoxia they can contact the study coordinator with appropriate documentation of the reason the titration was not done.

9.2.4. Participant privacy and confidentiality will be maintained by conducting the proposed activities in accordance with strict institutional guidelines, which require that formal approval be obtained from all appropriate committees before medical records are reviewed or patient contact is initiated. All study records are kept in password protected study folder and/or locked file cabinets. Individual participants are identified in all computer files and analyses only by a unique study number, which bears no relationship to personal identifiers including name, initials, address, telephone number, social security number, or patient number. Because of OSU's long-standing commitment to confidentiality, along with the requirements of the Ohio State Privacy Law, and more recently HIPAA, strict institutional procedures have been put in place to help maintain patient (subject) privacy. Note that OSU is compliant with HIPAA and all study procedures will be compliant and staff is trained in HIPAA requirements. Moreover, there is intensive orientation on the confidentiality of medical records and protected health information. Data sharing policies include the requirement that all "identifiers" be removed. All data are tracked in databases by anonymous but linkable study numbers. No identifiable information is explicitly released.

10. HUMAN SUBJECT PROTECTION

Similar for TOOL 1 and TOOL 2

10.1. Selection of subjects: Federal regulations at 45 CFR 46(a)(3) require the equitable selection of subjects. All patients admitted to the Medical ICU, who qualify based on the inclusion and exclusion criteria will be eligible to participate.

10.2. Vulnerable Populations

10.2.1. *Inclusion of Women:* Females who are older than 18 years of ages and who otherwise qualify under the inclusion/exclusion criteria will be actively recruited for this study. It is anticipated that the percentage of females within the study sample should reflect that of the study population. Women of childbearing age are considered because they are at risk for mechanical ventilation, as well as future treatment of this subpopulation may benefit from any knowledge gained by this clinical investigation. A urine pregnancy test is administered for all women of a childbearing age admitted to the ICU. If the urine pregnancy test is negative then they will be included in the study, if it is positive then they will be excluded per exclusion criteria. Females who are actively pregnant, as defined by the presence of positive urine or serum pregnancy test, or the patient's personal history of current pregnancy, will be excluded primarily because effects of varying supply of

oxygen in the fetus is not known. Therefore, it is unacceptable place them and their fetus at additional unnecessary risk.

10.2.2. *Inclusion of Children:* Only adults the age of 18 years or above will be recruited to this study. No children will be recruited.

10.2.3. *Inclusion of Minorities:* Individuals, either male or female, from the minority ethnic and/or racial groups described, and who otherwise would qualify under the inclusion/exclusion criteria, will be recruited for this study. Every effort will be made to recruit individuals from all ethnic groups, but such efforts will be hampered by the ethnic and racial demographics of the inpatients admitted to the Ohio State University Health System.

10.3. Informed Consent:

All participants in the study will be mechanically ventilated and in the Medical ICU. The study is time sensitive and oxygen titration needs to begin as soon as possible, preferably within an hour of endotracheal intubation. We will get informed consent from the patient/ LAR prior to randomization and initiation of the study, in all possible circumstances. However, in about 30- 40% patients we expect that at the time of enrollment the participants will be unable to give a full informed consent. We understand that getting full informed consent is a process and in this situation, we request a deferred informed consent / HIPPA authorization from the patient or the LAR.

The reason for requesting deferred consent is that the study cannot practically be carried out without this measure with scientific merit. The aim of the study is to achieve oxygen saturation within a time sensitive manner. In order to prevent excessive oxygen exposure we need to initiate oxygen titration within one hour after endotracheal intubation. This is important as the highest potential for hyperoxia is during the initial hours of mechanical ventilation. In about 30- 40% patients we expect that at the time of enrollment the participants will be unable to give a full informed consent. These are the situations, in the medical ICU, when there are many barriers to obtaining informed consent from potential candidates prior to the start of the study:

- Many subjects are admitted to the ICU by the rapid response team. These patients require immediate intubation for severe respiratory failure and have impaired cognitive function.
- For other subjects who undergo mechanical ventilation (MV) in the ICU, the situation is urgent and related to a sudden deterioration in clinical condition.
- In both the above situations, it would be unethical to delay intubation while attempting to obtain consent. Attempting to get consent in this situation is detrimental to work flow and interrupting healthcare staff's duties as well as hampering patient care.
- Patients in the medical ICU usually have many comorbid medical illnesses and may not have the cognitive capacity prior to intubation for giving fully informed consent.

- Some patients who will be enrolled in the study will be mechanically ventilated when they enter the ICU and under the influence of sedation. Due to sedation and narcotics given to the subject on the ventilator, these subjects may be deeply sedated and in the best situation drowsy but arousable. This is not an appropriate situation to gain consent.

- Obtaining consent from family members or LAR within one hour of intubation is also very challenging in some situations for this study. Rarely are family members present during a rapid response team call. Many other patients are transported to OSU via air or ground transport unaccompanied by family. This routinely happens at night and depending on the time of day and distance it may take several hours or days before the family arrives. Obtaining consent via FAX is also impractical for this study. Most families do not have access to a FAX in a timely manner. Also, many families are en route and cannot be contacted within a short timeframe.

Therefore in patients who are unable to give consent initially or do not have family members/ LARs present in hospital at the time of initiation, we request permission for a waiver for informed consent and HIPPA authorization until full informed consent/ HIPPA authorization can be obtained.

In the situations when we request a waiver, we will approach the LAR/ family at the earliest possible moment for a full informed consent/ HIPPA authorization:

- In the event that the LAR/ family denies consent, we will withdraw the patient from the study. Since we will only be collecting data, which is recorded in the process of ICU care; no additional or new data will be collected for research purposes.

- If the family member/ LAR gives consent then we will continue the subject's participation in the study. Then for that subject, at the earliest possible time that mechanical ventilation has been terminated and the participant is free from the influence of sedative medications the consenting process will be repeated to inform him of the study and confirm his permission to use his data for the research. He will be asked to sign on the same consent form/ HIPPA authorization. If he refuses at the time then we will withdraw him from the study and will not record his data.

- For patients enrolled in the study, if the family member/ LAR is not available in a reasonable period of time, we will attempt to contact them by phone

- There is a small possibility that the LAR is not present or has not visited the hospital, the consent will be taken from the patient after mechanical ventilation has been terminated and the participant is not under the influence of sedative medications. The capacity to consent will be determined the by the research coordinator or the PI whoever is present and taking the consent.

- If a participant refuses consent after discontinuing MV, or the LAR refuses at any time during the study, then his data will not be collected and will not be analyzed. No new levels of oxygenation are proposed, hence there should be no perceived threat to patient safety, but potential improvement in standard of care.

PANDEMIC Related Request: Given the current pandemic, visiting hours for patients without COVID 19 are still limited to few hours a day. In addition, travelling resources from long distance also have limitation. LAR's/ family members themselves having chronic diseases may want to avoid coming to the hospital. Given the above situation, we would like to request the ability to consent remotely via phone or internet.

11. **ADVERSE EVENTS:**

Assuring patient safety is an essential component of this protocol.

11.1. *Phase 1: NA*

11.2. *Phase 2 TOOL 1*

Hypoxemia: Minor hypoxemic event will be defined sustained hypoxemia within 90 minutes of FiO2 titration of Spo2 less than 88% for greater than 15 minutes, resolved with increase in FiO2 and or one time increase in PEEP.

Hypoxemia: Major hypoxemic event will be defined a sustained hypoxemia within 90 minutes of FiO2 titration of Spo2 less than 88% for greater than 15 minutes, requiring changes in multiple ventilator parameters, discontinuation from the ventilator and bag valve mask use or ventilator/ non- ventilator strategies for management of refractory hypoxemia.

11.3. *Phase 2 TOOL 2*

- Exclusion criteria designed to prevent enrollment of patients who are likely to need liberal oxygen supplementation for therapeutic reasons.
- Hypoxemia: Minor hypoxemic event will be defined sustained hypoxemia within 90 minutes of FiO2 titration of Spo2 less than 88% for greater than 15 minutes, resolved with increase in FiO2 and or one time increase in PEEP.
- Hypoxemia: Major hypoxemic event will be defined a sustained hypoxemia within 90 minutes of FiO2 titration of Spo2 less than 88% for greater than 15 minutes, requiring changes in multiple ventilator parameters, discontinuation from the ventilator and bag valve mask use or ventilator/ non- ventilator strategies for management of refractory hypoxemia.
- New onset arrhythmia after enrollment in the study associated with hypoxemia
- New onset shock after enrollment in the study (defined as lactate greater than 4, with new and escalating vasopressor use)
- Death in hospital
- Please see Appendix F for grading Adverse events (mild, moderate, severe)

12. **SERIOUS ADVERSE EVENTS:**

Section added for TOOL 2

12.1. Serious adverse event collection begins after randomization and study procedures have been initiated. If a patient experiences a serious adverse event prior to

starting study procedures, the event will NOT be collected. Study coordinator will report study procedure related adverse event within 24 hours of investigator awareness of the event. The medical monitor will make the determination of a serious adverse event.

As per the FDA and NIH definitions, a serious adverse event is any adverse event that results in one of the following outcomes:

- Death
- A life-threatening experience (that is, immediate risk of dying)
- Prolonged inpatient hospitalization or re-hospitalization

Based on the above, we would consider the following among the above as SAE:

- Major hypoxemic event: Sustained hypoxemia (SpO2 less than 88% for greater than 15 minutes) requiring changes in multiple ventilator parameters, discontinuation from the ventilator and Ambu bag use or ventilator/ non-ventilator strategies for management of refractory hypoxemia
- New onset arrhythmia after enrollment in the study associated with hypoxemia (only if associated with hemodynamic compromise)
- New onset shock after enrollment in the study (defined as lactate > 4, with new and escalating vasopressor use)
- Death in hospital

12.2. Serious adverse events will be collected until hospital discharge or first 30 days, whichever occurs first, regardless of the investigator's opinion of causation.

12.3. Determining Relationship of Adverse Events to Study Procedures: The Medical Monitor will work collaboratively with the study coordinator to determine if a serious adverse event has a reasonable possibility of having been caused by the study procedure. He will be asked to grade the strength of the relationship of an adverse event to study drug or study procedures as follows:

Definitely Related: The event follows: a) A reasonable, temporal sequence from a study procedure; and b) Cannot be explained by the known characteristics of the patient's clinical state or other therapies; and c) Evaluation of the patient's clinical state indicates to the monitor that the experience is definitely related to study procedures.

Probably or Possibly Related: The event should be assessed following the same criteria for "Definitely Associated". If in the investigator's opinion at least one or more of the criteria are not present, then "probably" or "possibly" associated should be selected.

Probably Not Related: The event occurred while the patient was on the study but can reasonably be explained by the known characteristics of the patient's clinical state or other therapies.

Definitely Not Related: The event is definitely produced by the patient's clinical state or by other modes of therapy administered to the patient.

Uncertain Relationship: The event does not meet any of the criteria previously outlined.

12.4. Unanticipated problems: Study coordinators will report Unanticipated Problems, regardless of severity, associated with study procedures within 24 hours to the investigator. These events will be noted and reported tot eh DSMB.

An unanticipated problem is defined as follows: any incident, experience, or outcome that meets all of the following criteria:

- Unexpected, in terms of nature, severity, or frequency, given the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and the characteristics of the subject population being studied;
- Related or possibly related to participation in the research, in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research;
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

13. **DATA SAFETY AND MONITORING BOARD**

Section added for TOOL 2

The study will be monitored by an OSU CCTS-supported Data and Safety Monitoring Board and an independent medical monitor.

The OSU CCTS-supported Data and Safety Monitoring Board will oversee the study. The DSMB will be established to ensure participant safety, ensure the validity and integrity of the data, monitor study progress, and make recommendations regarding appropriate protocol and operational changes which may have substantial effects upon the ultimate interpretation of the study. The DSMB will be comprised of experienced members with expertise in either the scientific field of study, clinical trials, statistics, research ethics and/or epidemiology three scientists who are independent of both the study investigators and the CCTS. The DSMB will review protocol - specific reports created by the research team. These standard reports will include an overview of study objectives, a review of actual and projected accrual rates, an evaluation of patient demographics for balance of randomization, weekly adherence data and a summary of the type, frequency, attribution, severity, seriousness and expectedness of adverse events. The study coordinator will have aggregated and unblinded data. The study coordinator will send deidentified data to the study statistician for analysis. If the DSMB needs to see unblinded data- they will be provided extracted data from the study coordinator. If needed by the DSMB, the statistician can be unblinded. The PI will present aggregated trial data (both arms together) updated to within 30 days of the DSMB meeting date.

Accruals, withdrawals, and protocol violations of enrollment will be reported at the DSMB meetings. DSMB also receive summary reports of the weekly checks of the EMR by the study coordinators that are designed assess protocol adherence. The DSMB will make recommendations to the Principal Investigator that could include actions of continuation, modification, suspension, or termination.

In providing oversight for the conduct of this study, the DSMB will meet at a minimum of every 6 months during the 18-month study to review all salient study information. Additional meetings may be scheduled as determined by the DSMB. All serious adverse events regardless of severity, attribution and/or expectedness will be reported to the DSMB and the Ohio State University IRB oversight committee in accordance with their reporting guidelines. The DSMB recommended actions and all pertinent regulatory information will be forwarded to the appropriate Institutional Review Board(s).

Medical Monitor: A medical monitor will be appointed. He will not be a member of the study team. He will be responsible for real-time monitoring of reports of serious adverse events submitted by the research personal to identify safety concerns quickly and to provide the DSMB with case-by-case reports of the serious adverse events. The medical monitor will be blinded and will make all determinations of severity and relatedness.

14. **POTENTIAL BENEFITS TO RESEARCH PARTICIPANTS OR OTHERS**

This study has the potential for benefits to the reduce time on excessive oxygen supplementation and potential adverse effects related to hyperoxia. Moreover, it can standardize practice of oxygen titration. This is not only beneficial to optimize standard of care abut also will potentially be cost effective in oxygen utilization. This study also gives the opportunity to utilize the expertise of respiratory therapists who are dedicated to ventilator management. Many respiratory therapist based automated protocols have been executed successfully with improved patient outcomes and process of care. E.g. weaning protocol. We expect that on successful completion, we can externally validate our decision support tool and algorithm for automated oxygen titration. Once externally validated this tool can serve for both, better utilization of physician time for other critical modalities of patient care and improved patient safety with regards to preventing hyperoxia. There will be no other direct benefit to the patients who voluntarily choose to participate in this study. The clinicians of record will determine all clinical care. There will be no monetary incentive for enrollment. Benefits will only be from the conclusions of the study and their impact on the future care similar patients.

15. IMPORTANCE OF KNOWLEDGE TO BE GAINED:

The completion of this study will help us to reduce potentially harmful oxygen exposure in mechanically ventilated patients. This contribution will be significant because completion of this study will demonstrate a safe, effective and pragmatic, approach to precisely titrate oxygen therapy during mechanical ventilation. This approach will leverage electronic alerts (e-alerts) derived from electronic medical records (EMR) to assist respiratory therapist who focus on mechanical ventilation. This simple strategy based on real time ascertainment of oxygenation by electronic media and “reminders” to respiratory therapists has substantial potential for widespread generalizability. It importantly addresses hyperoxia in early hours of mechanical ventilation. By maintaining safety, yet prioritizing titration, we can potentially lead

to earlier weaning and therefore substantial impact on the resource utilization and reduction in oxygen, mechanical ventilation and intensive care unit requirements will be achieved.

APPENDIX A

Interventional arm flow diagram for TOOL 1- Figure 1
Interventional arm decision support for TOOL 1- Figure 2

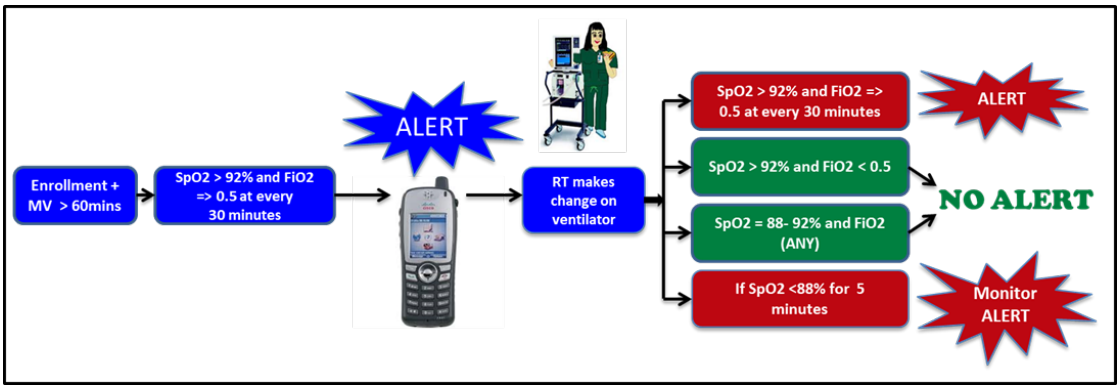


Figure 1. Interventional arm flow diagram for TOOL 1. Figure 1 shows the process of FiO2 titration in the intervention arm. Alert notification starts only after an hour of intubation. When the criteria for SpO2 and FiO2 are met as noted above, then a pager/ text alert is sent on the CISCO phone to the Respiratory Therapist (RT). SPO2 and FiO2 criteria for e-alert vs no e-alert are noted above. The bedside monitor will alarm if SpO2 drops below 88% for 5 minutes.

Hyperoxia	FiO_2 => 0.5 and SpO_2 > 92% for > 30mins	If FiO_2 => 0.7 & SpO_2 = 92% to 94% → reduce FiO_2 by 0.1
		If FiO_2 ≥ 0.7 and SpO_2 => 95% → reduce FiO_2 by 0.2 or PEEP by 2
		If FiO_2 ≥ 0.5 or 0.6→ reduce FiO_2 by 0.1
Optimal FiO_2 and SpO_2 Range	FiO_2 < 0.5 and SpO_2 > 92%	Make no change (There should be no alert)
	FiO_2 > 0.5 and SpO_2 < 92%	

APPENDIX B

Interventional arm flow diagram for TOOL 2- Figure 3

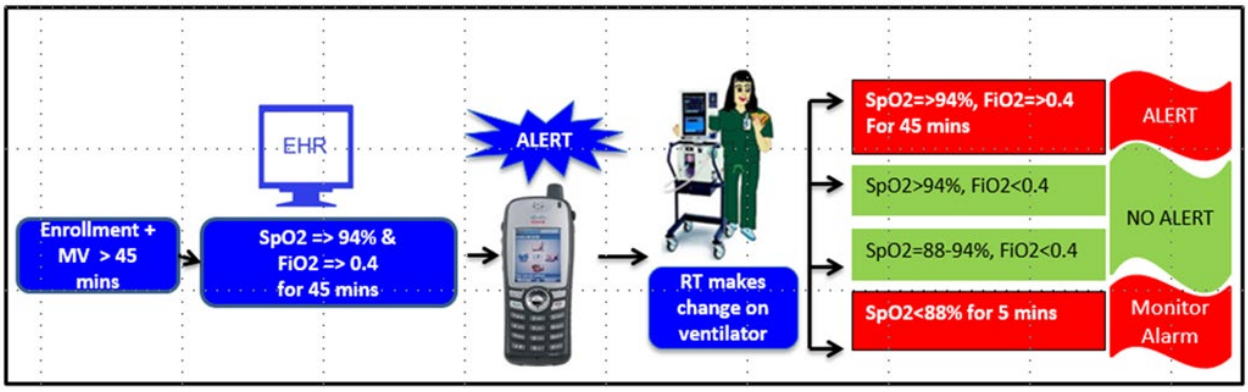


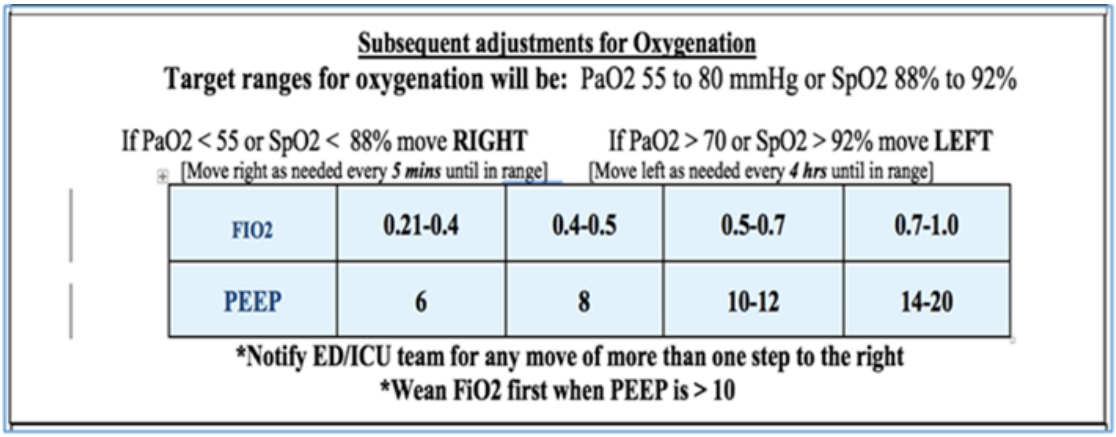
Figure 3. Interventional arm flow diagram for TOOL 2. Figure 3 shows the process of FiO2 titration in the intervention arm for TOOL 2. Alert notification starts only after 45 minutes of intubation. When the criteria for SpO2 and FiO2 are met as noted above, then a pager/ text alert is sent on the CISCO phone to the Respiratory Therapist (RT). SPO2 and FiO2 criteria for e-alert vs no e-alert are noted above. The bedside monitor will alarm if SpO2 drops below 88% for 5 minutes.

Interventional arm decision support for TOOL 2- Figure 4

DECISION SUPPORT TOOL		
HYPEROXIA	FiO2 => 0.4 and SpO2 => 94% for > 45 mins	If FiO2 < 0.7 then reduce FiO2 by 0.1 per alert
		If FiO2 => 0.7 then reduce FiO2 by 0.2 per alert
		PEEP management per ICU mechanical ventilation protocol
OPTIMAL FIO2 AND SPO2	SpO2 = 88-93%, SpO2 => 94% and FiO2 < 0.4	Make no change (There should be no alert)
HYPOXIA AFTER TITRATION	SpO2 less than 88% For atleast 5 minutes, FiO2 any value	Increase FiO2 by 0.2 → Inform MD → Next Steps per MD

Figure 4. Decision support created with directions for FiO2 titration for TOOL 2. Figure 4 shows decision support given to respiratory therapists with detailed directions for FiO2 titration for patients in the interventional arm. This was simplified from the decision support for TOOL1

Control arm ICU mechanical ventilation protocol – Figure 5 (used for TOOL 1 and TOOL 2)



Subsequent adjustments for Oxygenation

Target ranges for oxygenation will be: PaO2 55 to 80 mmHg or SpO2 88% to 92%

If PaO2 < 55 or SpO2 < 88% move **RIGHT** [Move right as needed every ***5 mins*** until in range]

If PaO2 > 70 or SpO2 > 92% move **LEFT** [Move left as needed every ***4 hrs*** until in range]

FIO2	0.21-0.4	0.4-0.5	0.5-0.7	0.7-1.0
PEEP	6	8	10-12	14-20

*Notify ED/ICU team for any move of more than one step to the right

*Wean FiO2 first when PEEP is > 10

Figure 5 Screen shot of the current ICU mechanical ventilation protocol. Figure 5 indicated the current ICU mechanical ventilation protocol with directions for oxygen titration.

APPENDIX C:

Flow Charts for Phase 1 – Figure 6 a and b

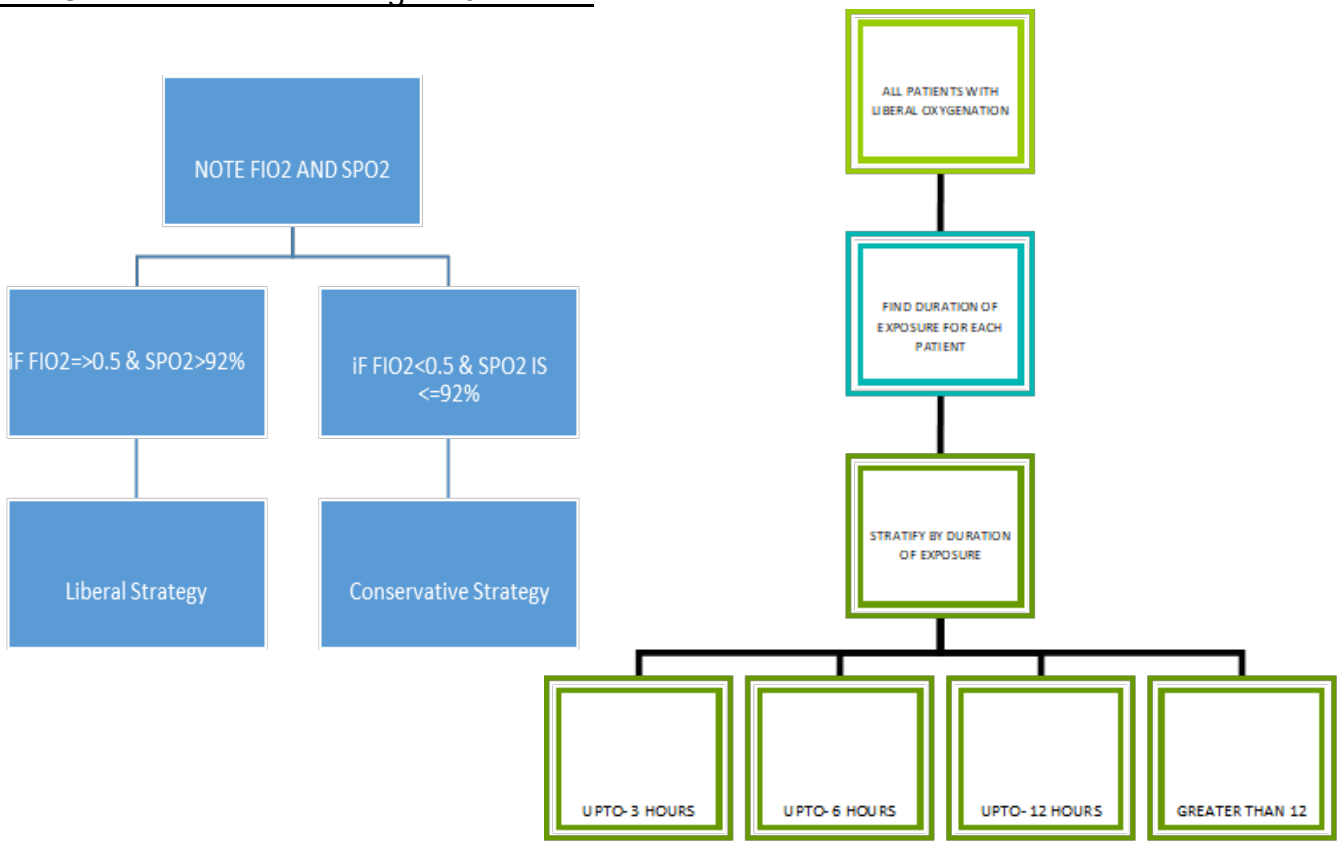
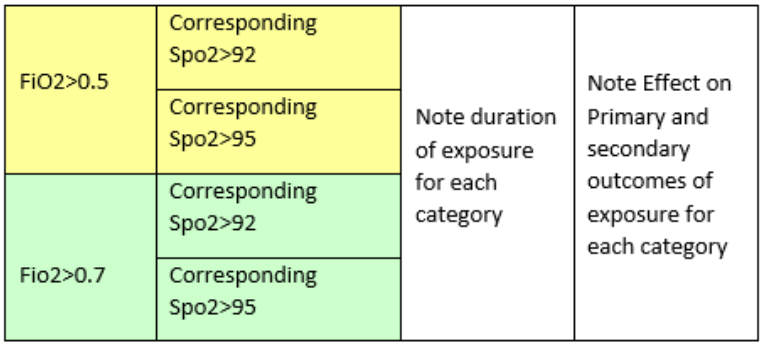


Figure 6 a and b, indicate flow diagram for Phase 1 chart review and definition for liberal and conservative oxygenation

APPENDIX D
Data and Outcome Variables for Phase 1

Variables	Measurement	Variables	Measurement
Demographics	Date of birth, gender, weight, height	Mechanical Ventilation	FiO2 (median, IQR)
	Date/time of hospital and ICU admission		PEEP (median, IQR)
	ICU admission Diagnosis		Tidal Volume (pre set and expired)
	Date/time of onset of mechanical ventilation		RR (median, IQR)
	Indication for mechanical ventilation		Plateau Pressure (median, IQR)
	Apache III scores at admission		Mean Airway Pressure (median, IQR)
	SOFA score on admission		Oxygenation Index (median, IQR)
	Advance Directive at admission		VD/VT
	Change in Advance directive during hospital course		Daily PaO2/FiO2 ratio (highest and lowest)
Physiologic	HR (median for 24 hours)	Relevant Therapy	NM blocker use (duration, dose)
	MAP (median for 24 hours)	Chest Imaging	Quadrant involvement

Outcome	Variables
	ICU/28 day mortality
	ICU stay (days)
	Hospital stay (days)
	28 ventilator free days
	Hospital Mortality



APPENDIX E:
Data Variables for TOOL 2

Variables	Measurement	Source
Demographics	Date of birth, gender, weight, height	Medical record
	Date/time of hospital and ICU admission	Medical record
	ICU admission Diagnosis	Medical record
	Date/time of onset of mechanical ventilation	Medical record
	Indication for mechanical ventilation	Medical record
	Apache III scores at admission	Medical record
	SOFA score on admission	Medical record
	Predicted hospital mortality	Medical record
	Advance Directive at admission	Medical record
	Change in Advance directive during hospital course	Medical record
Physiologic	HR (continuous, median for 24 hours)	Medical record
	MAP (continuous, median for 24 hours)	Medical record
	SpO2 (continuous, median for 24 hours)	Medical record
	FiO2 (continuous, median for 24 hours)	Medical record
Mechanical Ventilation	Time from Intubation to randomization	Medical record
	PEEP (continuous, median for 24 hours, IQR)	Medical record
	Tidal Volume (preset and expired)	Medical record
	RR (continuous, median for 24 hours, IQR)	Medical record
	Plateau Pressure (continuous, median for 24 hours, IQR)	Medical record
	Mean Airway Pressure (continuous, median for 24 hours, IQR)	Medical record
	Oxygenation Index (median, IQR)	Medical record
	VD/VT	Medical record

	P/F ratio (daily)	
	SpO2/FiO2 ratio (daily)	Medical record
	Mode of MV used and Duration	Medical record
	No of hypoxemia alarms (O2 sat <88% for 5 minutes)	Medical record
Relevant Therapy	NM blocker use (duration, dose)	Medical record
	Vasopressor use (duration, type)	
	ABG: pH, paco2, pao2 (median, over 24 hour)	Medical record
	Hob, HCT (nadir)	Medical record
Chest imaging	Chest X-ray - Quadrant involvement	Medical record
Outcome	Proportion of time during mechanical ventilation spent with FiO2≥0.4 and Spo2≥94%.	Medical record
	Proportion of time during mechanical ventilation spent with SpO2<88%	Medical record
	Duration of mechanical ventilation	Medical record
	ICU stay (days)	Medical record
	Hospital stay (days)	Medical record
	Hospital mortality	Medical record

APPENDIX F

Guidelines to the Medical Monitor for grading adverse events

Adverse events	**Definition**	**Action taken to resolve**	**Grade**
Minor hypoxemic event	Sustained hypoxemia within 90 minutes of FiO2 titration of Spo2 less than 88% for greater than 15 minutes, resolved with increase in FiO2 and or one time increase in PEEP	Increase in FiO2 by 0.1	MILD
		Increase in FiO2 by 0.2	MILD
		Increase in FiO2 0.1 or 0.2 and any increase in PEEP	MODERATE
		Increase in FiO2 >0.2 and any one time increase in PEEP (<=2 cms	SEVERE
Major hypoxemic event	Sustained hypoxemia within 90 minutes of FiO2 titration of Spo2 less than 88% for greater than 15 minutes, requiring changes in multiple ventilator parameters, discontinuation from the ventilator and bag valve mask use or ventilator/ non-ventilator strategies for management of refractory hypoxemia	Increase in FiO2 >0.2 and any one time increase in PEEP > 2cms	MILD
		Increase in FiO2 >0.2 and any one time increase in PEEP > 2cms combined with any other vent parameter changes- Change in I:E ratio, peak flow, recruitment maneuver; change in ventilator mode (PRVC/ AC/PC/ bi-level)	MODERATE
		Any of the above changes along with discontinuation of the ventilator, oxygenation with bag, mask valve ventilation	MODERATE

		Any of the above events, and need for prone position; inhaled vasodilator or Extra corporeal oxygenation	SEVERE
New onset arrhythmia	New onset arrhythmia after enrollment in the study associated with hypoxemia	Resolved with increase in FiO2	MILD
		New onset arrhythmia (not resolved with increase in FiO2 or less than 2 cm change in PEEP) causing worsening hypoxemia	MODERATE
		New onset arrhythmia with hemodynamic compromise	SEVERE
New onset shock	New onset shock associated with hypoxemia (Spo2 less than 88% for atleast 15 mins or PaO2 less than 60) after enrollment in the study (defined as lactate greater than 4, with new and escalating vasopressor use)	New onset shock improving by increasing FiO2 or other MV measures	MILD
		New onset shock responding to increased FiO2 or other MV measures and fluids (in addition to initial vasopressor use)	MODERATE
		New onset shock not resolving by any of the above, needing third line pressors	SEVERE

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